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Symposium

Neurobiology of Escalated Aggression and Violence

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Psychopathological violence in criminals and intense aggression in fruit flies and rodents are studied with novel behavioral, neurobiological, and genetic approaches that characterize the escalation from adaptive aggression to violence. One goal is to delineate the type of aggressive behavior and its escalation with greater precision; second, the prefrontal cortex (PFC) and brainstem structures emerge as pivotal nodes in the limbic circuitry mediating escalated aggressive behavior. The neurochemical and molecular work focuses on the genes that enable invertebrate aggression in males and females and genes that are expressed or suppressed as a result of aggressive experiences in mammals. The *fruitless* gene, immediate early genes in discrete serotonin neurons, or sex chromosome genes identify sexually differentiated mechanisms for escalated aggression. Male, but not female, fruit flies establish hierarchical relationships in fights and learn from previous fighting experiences. By manipulating either the *fruitless* or *transformer* genes in the brains of male or female flies, patterns of aggression can be switched with males using female patterns and vice versa. Work with *Sts* or *Sry* genes suggests so far that other genes on the X chromosomes may have a more critical role in female mouse aggression. New data from feral rats point to the regulatory influences on mesocortical serotonin circuits in highly aggressive animals via feedback to autoreceptors and via GABAergic and glutamatergic inputs. Imaging data lead to the hypothesis that antisocial, violent, and psychopathic behavior may in part be attributable to impairments in some of the brain structures (dorsal and ventral PFC, amygdala, and angular gyrus) subserving moral cognition and emotion.

Key words: aggression; alcohol; genetics; learning; prefrontal cortex; serotonergic 1A receptor; serotonin; sex difference

Research on aggression and violence is pursued by social and biological scientists with profoundly divergent approaches. At present, the schism between these approaches promises to be overcome by advancing our knowledge of the molecular events through which social experiences sculpt future aggressive acts. Insights into the gene–environment interactions are critical for the way in which the criminal justice and the public health systems deal with aggression and violence. Neurobiological research of aggressive behavior is emerging from several shameful episodes during the past century ranging from the eugenics movement to lobotomies to stigmatizing individuals with phenologically defined biomarkers (Valenstein, 1987). As a matter of fact, the *World Report on Violence and Health* (2002) by the World Health Organization ignores the neuroscience approach to these

behaviors altogether (Krug et al., 2002). Here we point to several emerging successes in behavioral and molecular biology of aggression research that may have important implications not only for diagnosis, prevention, and treatment but also for guidance of public and judicial policies.

Aggression as an adaptive behavior in males and females: quantitative ethological analysis

Classic ethological studies have focused on aggression because this behavior is typical for both invertebrate and vertebrate species during particular situations of conflict. The study of the phylogeny, ontogeny, and functional significance of these complex behavioral adaptations in different kinds of aggressive confrontations provides the foundation for neurobiological analyses. The salient acts, postures, and communicative signals of aggressive behavior follow an intricate temporal and sequential organization, some are common to males and females, and others are sexually dimorphic (Nilsen et al., 2004; Miczek et al., 2007). In a newly studied invertebrate model, male fruit flies (*Drosophila melanogaster*) establish hierarchical relationships in fights, whereas female flies do not. Like mammals, flies learn from previous fighting experiences and use this information for establishing and maintaining hierarchical relationships (Yurkovic et al.,

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2006). In adult male and female mice, exposure to androgenic steroids during critical prenatal and postnatal periods are among the distal determinants of subsequent aggressive behavior, and these influences during early development are readily seen in adult male and female aggression in mice (Vom Saal and Bronson, 1978; Mann and Svare, 1983). An important task is to extend the insights from species-normative aggression to clinical concerns with pathological aggression.

The need for valid experimental models of escalated aggression

Examples from clinical research on aggressive behavior illustrate the focus on behavioral phenotypes that exceed the species-normative patterns and represent behavioral pathologies (Raine and Yang, 2006). New experimental models of escalated aggressive behavior in mice, hamsters, and rats attempt to translate more adequately to clinically problematic violent outbursts (Miczek et al., 2004, 2007; Haller and Kruk, 2006; Nelson and Trainor, 2007). Many experimental models rely on noxious environmental stimuli, neural lesions, or pharmacological or genetic manipulations to engender aggressive behavior in otherwise placid laboratory animals (de Boer and Koolhaas, 2005). For example, the preferential use of mice of the 129 Sv strain for targeted gene manipulations triggers aggressive behavior in a strain that, uncharacteristic for this pugnacious species, usually does not fight (Miczek et al., 2001). In extension of the original account in mice (Ginsburg and Allee, 1942), a new model uses feral-derived resident rats that escalate their aggressive behavior as a result of repeated victories in aggressive confrontations with intruders (i.e., short latency, high frequency and intensity, persistent attacks that are indiscriminate of opponent, impervious to signals of submission, and potentially injurious) (de Boer and Koolhaas, 2005). This methodological approach highlights the rewarding nature of aggressive behavior that has begun to be characterized in terms of its neurobiology in mice (Fish et al., 2002, 2005, 2007).

Ethical dilemma of aggression research

To be clinically relevant, experimental model systems for aggressive behavior need to be valid, and this development crystallizes a central ethical dilemma of aggression research, namely harm and injury. Two countervailing principles govern this research: face validity is achieved when the behavior is potentially harmful and injurious, yet, at the same time, every ethical research guideline emphasizes the reduction and avoidance of the risk to be harmed or injured. Each research question and protocol needs to probe how much harm and injury is necessary or acceptable to generate scientifically valid information that can be translated into concerns of the public health system. Although this discussion focuses primarily on mammals, it is pertinent to all species.

The genetics of learning to be aggressive

New studies show how the *fruitless* gene in *D. melanogaster*, which has been shown previously to be necessary and sufficient in determining whether a fly courts males or females, is also a critical determinant for how flies fight. By manipulating either the *fruitless* or *transformer* genes in the brains of male or female flies, patterns of aggression can be switched with males using female patterns of aggression or females using male patterns (Vrontou et al., 2006). Male protein products of *fruitless* (Fru^M) normally are found in 20 clusters of neurons in male CNS. Mechanistically, the expression of Fru^M must occur in a particular one of these 20 clusters of neurons in female flies to make the females fight like

males (Y. B. Chan and E. A. Kravitz, unpublished observations) (Kimura et al., 2005). Furthermore, Certel, Kravitz, and coworkers have demonstrated that the amine octopamine, the invertebrate homolog to norepinephrine, is involved in the behavioral choice between courtship and aggression in male flies (Certel et al., 2007) (S. J. Certel, unpublished observations). Of the ~80 octopamine neurons normally found in the fly CNS, three within the subesophageal ganglion show colocalization of the amine with Fru^M . Eliminating Fru^M expression in these three neurons by either feminizing the neurons in otherwise male brains or eliminating Fru^M by RNA interference yields the same behavioral phenotype as eliminating octopamine; male flies have difficulty determining whether to court or fight other males.

Sex chromosome genes and female aggression

In complement to the early hypothesis that the *Sry* (sex determining region Y) gene, located on the Y chromosome, acted as a candidate gene for differentiating aggression between sexes and among strains of mice (Maxson, 1996), Rissman and colleagues investigate *Sry* and another sex chromosome candidate gene, *Sts* (steroid sulfatase) (E. F. Rissman, unpublished data). This latter gene encodes the steroid sulfatase enzyme; it is located on the pseudoautosomal region of the Y chromosome and is expressed in both sexes. It is pivotal in the regulation of neurosteroid biosynthesis and altered brain activity of *Sts*, attributable to either genetic (Le Roy et al., 1999) or pharmacological (Nicolas et al., 2001) manipulations, and is correlated with levels of aggression among male mice.

Although resting brain levels of *Sts* are similar in both sexes, it increases dramatically in females after parturition and during lactation, corresponding to the onset of maternal aggression in many species. Rissman and coworkers hypothesized that *Sts* may exert a critical role in aggression expressed by females, but data from females with sex chromosome aneuploidy appear negative so far. Ongoing work using females that have a Y chromosome with spontaneous deletion of the *Sry* testes determining gene (referred to as Y^-) shows that the *Sry* gene is not needed for enhanced aggression when a resident female confronts an intruder female. Moreover, females with XY^- chromosome complements initiate offensive attacks on intruders faster than XX females (Gatewood et al., 2006). So far, this work shows that, although sex chromosome complement is involved in aggression, an X or Y gene other than *Sts* or *Sry* may have more critical roles in female aggression.

Serotonin—revisited

Brain serotonin (5-HT) has been implicated in the neurobiological mechanisms of aggression and violence more than any other molecule in the brain (Miczek et al., 2002, 2007; Kravitz and Huber, 2003). The early proposal of a tropotrophic action of this evolutionary ancient indolamine was extended to a calming effect on impulsively aggressive behavior, and this characterization was supported by correlational data from low CSF metabolite levels and blunted responses to serotonergic drug challenges in violent individuals (Linnoila et al., 1983; Coccaro, 1989). Recent data confirm lower levels of release of 5-HT in the nucleus accumbens and in prefrontal cortex (PFC) in rats with extensive experiences of aggressive behavior (Van Erp and Miczek, 2000; de Boer et al., 2003; Ferrari et al., 2003). Tonic brain levels of 5-HT decrease as a consequence of acquiring repeated victorious experiences. In contrast, the level of adaptive aggressive behavior is positively related to basal CSF concentrations of 5-HT in wild-type rats (Van der Vegt et al., 2003a,b). These data point to opposite roles

of mesocortical serotonin activity in adaptive and escalated forms of aggressive behavior.

The regulation of 5-HT release from serotonergic neurons via 5-HT_{1A} and 5-HT_{1B} autoreceptors and via GABAergic and glutamatergic input to these neurons have emerged as candidate mechanisms for the transition between adaptive and escalated types of aggressive behavior. Evidence points to potent and selective anti-aggressive effects of 5-HT_{1A} and 5-HT_{1B} receptor agonists on both somatodendritic autoreceptors and on postsynaptic receptors in male and female rodents (de Almeida and Lucion, 1997; de Boer and Koolhaas, 2005; Olivier and Van Oorschot, 2005; Bannai et al., 2007). Highly aggressive rats are characterized by upregulated somatodendritic 5-HT_{1A} and terminal 5-HT_{1B} autoreceptor (Caramaschi et al., 2007), and this activity can be further enhanced by victorious aggressive experiences. Based on their recent findings, de Boer and colleagues hypothesize that the enhanced inhibitory autoreceptor function is a normal compensatory adaptation to the more reactive state of the brain 5-HT system in highly aggressive animals. They further speculate that an excessive activation (i.e., overshoot) of an autoreceptor brake may be a causative link in the cascade of events leading to the hypofunction of 5-HT neurons that characterizes violent and pathological forms of aggressive behavior.

5-HT receptor gene expression in PFC

In rodents, 5-HT₁ and 5-HT₂ receptor genes are expressed at lower levels in the PFC of individuals who engage in escalated aggression after consumption of alcohol relative to those who fight at a species-typical level (Chiavegatto et al., 2007). Intact alcohol-heightened and other escalated forms of aggression are potentially inhibited by activation of 5-HT_{1B} receptors in subregions of the prefrontal cortex, possibly involving terminal autoreceptors or postsynaptic heteroreceptors (Faccidomo et al., 2005; de Almeida et al., 2006). If this is attributable to actions on postsynaptic receptors, compromised glutamatergic feedback from the prefrontal cortex to the raphe nuclei may serve as a necessary link for the expression of escalated aggression to be expressed. A focus on receptor pools in the prefrontal cortex is consistent with imaging data obtained from violent psychopaths, although in the latter case the anatomical resolution is more limited.

Brain systems common to violence and moral decision making

An increasing body of brain imaging research is documenting functional and structural brain impairments in antisocial and violent populations (Raine and Yang, 2006). Recent imaging research also is beginning to elucidate the neural correlates of moral decision making in normal individuals (Greene et al., 2001; Moll et al., 2005). Key areas found to be functionally or structurally impaired in antisocial populations include dorsal and ventral regions of the PFC, amygdala, hippocampus, angular gyrus, anterior cingulate, and temporal cortex (Raine and Yang, 2006). Regions most commonly activated in moral judgment tasks consist of the polar/medial and ventral PFC, amygdala, angular gyrus, and posterior cingulate (Raine and Yang, 2006). Although the overlap is by no means complete, some common ground exists between the neural circuitry underlying antisocial, violent behavior and moral decision making. Raine hypothesizes that the rule-breaking behavior common to antisocial, violent, and psychopathic individuals may in part be attributable to impairments in some of the structures (dorsal and ventral PFC, amygdala, and angular gyrus) subserving moral cognition and emotion. If of-

fenders are not fully responsible for the source of the brain dysfunction that impairs their moral decision making, this raises significant neuroethical issues regarding the appropriate level of punishment for those who show morally inappropriate acts.

Discussion

A research agenda should consider the following points emanating from the recent findings in various model systems.

(1) Advances in understanding of experience-dependent and sexually dimorphic gene expression need to be translated into the clinical practice of diagnosing and treating pathologically violent individuals. The more accessible invertebrate and rodent model systems demonstrating gene–environment interactions should enlighten the search for the primate counterparts of these mechanisms.

(2) Interdisciplinary rivalries are rendered irrelevant as the molecular mechanisms of salient social experiences and learning during aggressive confrontations are deciphered. The next step for the study of aggressive behavior should be to elucidate how the molecular mechanisms underlying these salient experiences interact with genetic and environmental factors that predispose some individuals to engage in escalated aggressive behavior.

(3) Mesocortical serotonin circuits are intricately regulated via feedback from autoreceptors and via GABAergic and glutamatergic inputs. Future work must take into account the regional and temporal specificity of the molecular changes taking place during the transition from adaptive to escalated aggressive behavior.

(4) Neuroethical concerns require discussion in open discourse among representatives of the criminal justice system, psychiatry, neuroscience, and the social sciences.

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